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CLAIMS

What is claimed is:

1. A method of diagnosing an miR15 or miR16 mediated cancer in
5 a subject, comprising measuring the level of miR15 or miR16 gene product in a sample derived from the subject, wherein a lower level of miR15 or miR16 gene product in the sample relative to the level of miR15 or miR16 gene product in a control sample, indicates the presence of the miR15 or miR16 mediated cancer.
- 10 2. The method of claim 1, wherein the level of miR15 or miR16 gene product is measured with an assay selected from the group consisting of northern blot analysis, in situ hybridization, and quantitative reverse transcriptase polymerase chain reaction.
- 15 3. The method of claim 1, wherein the miR15 or miR16 gene product is selected from the group of gene products having the sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4.
- 20 4. The method of claim 1, wherein the miR15 or miR16 mediated cancer is chronic lymphocytic leukemia or prostate cancer.
- 25 5. A method of diagnosing an miR15 or miR16 mediated cancer in a subject, comprising analyzing an miR15 or miR16 gene in a sample derived from the subject, wherein detection of one or more deletions or mutations in the miR15 or miR16 gene in the sample derived from the subject relative to the miR15 or miR16 gene in a control sample, indicates the presence of the miR15 or miR16 mediated cancer.
- 30 6. The method of claim 5, wherein the one or more deletions or mutations are analyzed with an assay selected from the group consisting of

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Southern blot hybridization, sequence analysis, and single strand conformational polymorphism.

7. The method of claim 5, wherein the miR15 or miR16 mediated
5 cancer is chronic lymphocytic leukemia or prostate cancer.

8. A method of diagnosing an miR15 or miR16 mediated cancer in
a subject, comprising measuring miR15 or miR16 gene copy number in a
sample derived from the subject, wherein a reduction in miR15 or miR16 gene
10 copy number to one or zero, indicates the presence of the miR15 or miR16
mediated cancer.

9. The method of claim 8, wherein the reduction in gene copy
number is measured by analyzing the loss of heterozygosity of the D13S273 or
15 D13S272 microsatellite markers on 13q14, wherein a loss of heterozygosity at
the D13S273 or D13S272 microsatellite markers indicates the presence of the
miR15 or miR16 mediated cancer.

10. The method of claim 9, wherein the loss of heterozygosity is
20 measured by analyzing the loss of heterozygosity of the D13S1150 or D13S273
microsatellite markers.

11. The method of claim 10, wherein the loss of heterozygosity is
measured by analyzing the loss of heterozygosity of the locus Alu18 or
25 D13S273 microsatellite marker.

12. The method of claim 8, wherein the miR15 or miR16 gene copy
number is measured by Southern blot hybridization.

13. The method of claim 8, wherein the miR15 or miR16 mediated
30 cancer is chronic lymphocytic leukemia or prostate cancer.

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14. A method of treating an miR15 or miR16 mediated cancer in a subject in need of such treatment, comprising administering to the subject an effective amount of an isolated miR15 or miR16 gene product such that proliferation of miR15 or miR16 mediated cancer cells is inhibited.

15. The method of claim 14, wherein the miR15 or miR16 mediated cancer is chronic lymphocytic leukemia or prostate cancer.

16. The method of claim 14, wherein the isolated miR15 or miR16 gene product is administered by transfection of cells of the subject.

17. The method of claim 16, wherein the cells are hematopoietic stem cells, chronic lymphocytic leukemia cells or prostate cancer cells.

18. The method of claim 14, wherein the isolated miR15 or miR16 gene product is administered to the subject parenterally or enterally.

19. The method of claim 18, wherein the enteral administration is oral, rectal, or intranasal.

20. The method of claim 18, wherein the parenteral administration is selected from the group consisting of intravascular administration, peri- or intra-tissue injection, subcutaneous injection or deposition including subcutaneous infusion, direct application, and inhalation.

21. The method of claim 20, wherein the intravascular administration is selected from the group consisting of intravenous bolus injection, intravenous infusion, intra-arterial bolus injection, intra-arterial infusion and catheter instillation into the vasculature.

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22. The method of claim 20, wherein the peri- and intra-tissue injection is selected from the group consisting of peri-tumoral and intra-tumoral injection, intra-retinal injection, or subretinal injection.

5 23. The method of claim 20, wherein the subcutaneous injection or deposition comprises infusion by an osmotic pump.

24. The method of claim 20, wherein the direct application comprises application by catheter, retinal pellet, suppository, an implant comprising a porous material, an implant comprising a non-porous material, or a material
10 comprising a gelatinous material.

25. The method of claim 14, wherein the isolated miR15 or miR16 gene product is administered as naked RNA, in conjunction with a delivery
15 reagent, or as a nucleic acid comprising sequences which express the miR15 or miR16 gene product.

26. The method of claim 25, wherein the nucleic acid comprising sequences which express the miR15 or miR16 gene product is a recombinant
20 plasmid or recombinant viral vector.

27. The method of claim 26, wherein the recombinant plasmid or recombinant viral vector comprises a U6 promoter, an H1 promoter, or a cytomegalovirus promoter.
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28. The method of claim 26, wherein the recombinant viral vector is an adenovirus vector, an adeno-associated virus vector, a retroviral vector, or a herpes virus vector.

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29. The method of claim 28, wherein the retroviral vector is selected from the group consisting of *lentiviral* vectors, Rhabdoviral vectors, and murine leukemia virus vectors.

5 30. The method of claim 14, wherein the isolated miR15 or miR16 gene product is administered in conjunction with a lipophilic reagent, lipofectin, lipofectamine, cellfectin, polycations, or liposomes.

10 31. The method of claim 30, wherein the liposomes comprise an opsonization-inhibiting moiety.

15 32. The method of claim 30, wherein the liposomes comprise a ligand which targets the liposomes to a chronic lymphocytic leukemia cell or prostate cancer cell.

 33. The method of claim 14, wherein the subject has a tumor, and the effective amount of an isolated miR15 or miR16 gene product is at least about 10 micrograms/gram of tumor mass.

20 34. The method of claim 33, wherein the effective amount of an isolated miR15 or miR16 gene product is at least about 60 micrograms/gram of tumor mass.

25 35. The method of claim 33, wherein the effective amount of an isolated miR15 or miR16 gene product is at least about 100 micrograms/gram of tumor mass.

30 36. The method of claim 33, wherein the effective amount of an isolated miR15 or miR16 gene product is between about 10-500 micrograms/gram of tumor mass.

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37. The method of claim 14, wherein the effective amount of an isolated miR15 or miR16 gene product is from about 5 to 3000 micrograms/kg body weight of the subject.

5 38. The method of claim 37, wherein the effective amount of an isolated miR15 or miR16 gene product is preferably between about 700 - 1000 micrograms/kg body weight of the subject.

39. The method of claim 14, wherein the effective amount of an
10 isolated miR15 or miR16 gene product is greater than about 1000 micrograms/kg body weight of the subject.

40. A method of treating an miR15 or miR16 mediated cancer in a subject in need of such treatment, comprising the steps of:

15 1) isolating cells from the subject;

 2) transfecting the cells with a nucleic acid comprising sequences encoding an effective amount of an miR15 or miR16 gene product; and

 3) reimplanting the transfected cells into the subject, such
20 that proliferation of miR15 or miR16 mediated cancer cells in the subject is inhibited.

41. The method of claim 40, wherein the miR15 or miR16 mediated cancer is chronic lymphocytic leukemia or prostate cancer.
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42. The method of claim 41, wherein expression of the miR15 or miR16 gene product in the transfected cells is confirmed prior to reimplantation of the transfected cells into the subject.

30 43. The method of claim 40, wherein stable integration of the nucleic acid comprising sequences encoding an effective amount of an miR15 or miR16

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gene product into the genome of the transfected cell is confirmed prior to reimplantation of the transfected cells into the subject.

44. The method of claim 40, wherein the nucleic acid comprising
5 sequences encoding an effective amount of an miR15 or miR16 gene product comprises a recombinant plasmid or recombinant viral vector.

45. The method of claim 44, wherein the recombinant plasmid or
recombinant viral vector comprises a U6 promoter, an H1 promoter, or a
10 cytomegalovirus promoter.

46. The method of claim 45, wherein the recombinant viral vector is
an adenovirus vector; an adeno-associated virus vector; a retroviral vector, or a
herpes virus vector.
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47. The method of claim 46, wherein the retroviral vector is selected
from the group consisting of *lentiviral* vectors, Rhabdoviral vectors, and murine
leukemia virus vectors.

48. The method of claim 40, wherein the transfected cells are chronic
20 lymphocytic leukemia cells or prostate cancer cells.

49. The method of claim 40, wherein the transfected cells are
hematopoietic stem cells.
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50. A method of inhibiting proliferation of miR15 or miR16
mediated cancer cells in a subject, comprising administering to the miR15 or
miR16 mediated cancer cells an effective amount of an isolated miR15 or
miR16 gene product.
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51. The method of claim 50, wherein the miR15 or miR16 mediated cancer cells comprise chronic lymphocytic leukemia cells or prostate cancer cells.

5 52. The method of claim 50, wherein the isolated miR15 or miR16 gene product is administered by transfection of the miR15 or miR16 mediated cancer cells.

53. The method of claim 50, wherein the isolated miR15 or miR16
10 gene product is administered as naked RNA, in conjunction with a delivery reagent, or as a nucleic acid comprising sequences which express the miR15 or miR16 gene product.

54. The method of claim 53, wherein the nucleic acid comprising
15 sequences which express the miR15 or miR16 gene product is a recombinant plasmid or recombinant viral vector.

55. The method of claim 54, wherein the recombinant plasmid or
20 recombinant viral vector comprises a U6 promoter, an H1 promoter, or a cytomegalovirus promoter.

56. The method of claim 54, wherein the recombinant viral vector is
an adenovirus vector, an adeno-associated virus vector, a retroviral vector, or a herpes virus vector.

25 57. The method of claim 56, wherein the retroviral vector is selected from the group consisting of *lentiviral* vectors, Rhabdoviral vectors, and murine leukemia virus vectors.

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58. The method of claim 50, wherein the isolated miR15 or miR16 gene product is administered in conjunction with a lipophilic reagent, lipofectin, lipofectamine, cellfectin, polycations, or liposomes.

5 59. The method of claim 58, wherein the liposome comprises an opsonization-inhibiting moiety.

60. The method of claim 58, wherein the liposome comprises a ligand which targets the liposome to a chronic lymphocytic leukemia cell or
10 prostate cancer cell.

61. A pharmaceutical composition comprising an isolated miR15 or miR16 gene product and a pharmaceutically acceptable carrier. ✓

15 62. The pharmaceutical composition of claim 61, wherein the isolated miR15 or miR16 gene product is encapsulated in a liposome.

63. The pharmaceutical composition of claim 62, wherein the liposome comprises an opsonization-inhibiting moiety.
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64. The pharmaceutical composition of claim 62, wherein the liposome comprises a ligand which targets the liposome to a chronic lymphocytic leukemia cell or prostate cancer cell.

25 65. The pharmaceutical composition of claim 61, wherein the isolated miR15 or miR16 gene product is resistant to degradation by nucleases.

66. The pharmaceutical composition of claim 65, wherein the isolated miR15 or miR16 gene product comprises one or more ribonucleotides
30 which are modified at the 2' position.

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67. The pharmaceutical composition of claim 66, comprising miR15 or miR16 gene products in which each ribonucleotide is a 2'-modified ribonucleotide.

5 68. The pharmaceutical composition of claim 66, wherein the one or more ribonucleotides which are modified at the 2' position are modified at the 2' position with fluoro, amino, alkyl, alkoxy, or O-allyl groups.

69. The pharmaceutical composition of claim 66, wherein the one or
10 more ribonucleotides which are modified at the 2' position are of the formula 2'AR-nucleotide, wherein:

A is oxygen or a halogen (preferably fluorine, chlorine or bromine); and

R is hydrogen or straight or branched chain C₁₋₆ alkyl;

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provided that when A is a halogen, then X and R are omitted.

70. The pharmaceutical composition of claim 66, wherein the one or more ribonucleotides which are modified at the 2' position is a 2'-O methyl
20 ribonucleotide.

71. A pharmaceutical composition comprising a nucleic acid encoding an isolated miR15 or miR16 gene product, and a pharmaceutically acceptable carrier.

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72. The pharmaceutical composition of claim 71, wherein the nucleic acid is encapsulated in a liposome.

73. The pharmaceutical composition of claim 72, wherein the
30 liposome comprises an opsonization-inhibiting moiety.

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74. The pharmaceutical composition of claim 72, wherein the liposome comprises a ligand which targets the liposome to a CLL or prostate cancer cell.